REMARKS

Rejections under 35 U.S.C. §103

The Examiner has maintained the rejection of claims 1, 3-7, 9, 10, 14, 15, 18 and 19 under 35 U.S.C. §103 as being obvious over Itokawa et al.; of claims 1, 3, 9 and 10 as being obvious over Naruse et al.; of claims 2 and 13 as being obvious over Itokawa et al. or Naruse et al. in view of Horowitz et al.; and of claims 8 and 11 has being obvious over Itokawa et al. and Naruse et al. in view of Vater et al. Applicants traverse these rejections and withdrawal thereof is respectfully requested.

In the Advisory Action, the Examiner asserts that Applicants' previous arguments were insufficient to overcome the rejections for the following points, which are addressed in turn.

1) **Reduction in viral titre** The Examiner asserts that recited reduction in viral titer is only equivalent to viral inactivation for the particular disclosed experiment. The Examiner asserts that if initial viral titer is higher than that disclosed in the experiments, a 10^4 reduction will not result in full inactivation. Claim 1 has been amended to more clearly recite

> A method of rendering a purified product isolated from blood or a biotechnologically produced product substantially free of lipid-enveloped viruses by reducing the viral titer by a factor of approximately $>10^4$, which comprises....

In Example 5 of the specification, herpes virus (HSV-1) was treated with surfactin. The viral titer of dropped from an initial titer of 5.1 X 10^6 ID_{50} (50% infectious dose)/ml to zero infectious particles/ml, which corresponded to a reduction of viral titer by a factor of 10^5 within 60 minutes.

Example 6 shows the inactivation of surfactin lipopeptide on a variety of lipid-enveloped viruses. See Table 1 on page 19 for a summary of the results. After 1 to 2 hours of treatment less than 0.02% (i.e. substantially free of virus) of the initial titers, which ranged from 4.2 X10^4 ID_{50}/ml (HSV-2) to 7.0 X10^7 ID_{50}/ml (SFV), was detected. These results demonstrate that the viral titer was reduced by a factor of 10^4 to 10^7.

Examples 11 and 12 similarly demonstrate the reduction of viral titer. In Examples 11 and 12, virus was inactivated in a protein solution. The initial viral titer was 1.6 X 10^5 $TCID_{50}$/ml ($TCID_{50}$= does infecting 50% of the tissue culture). After 120 minutes (Example 11) and after 20 minutes (Example 12), no infectious particles could be detected, which corresponds to a reduction in viral titer by a factor of 10^5 (or a drop in infectiousness of "5 logs", i.e. $5\log_{10}$ $TCID_{50}$). Example 13 presents similar reductions in viral titer (reductions of 4.5 to 5.4 logs).

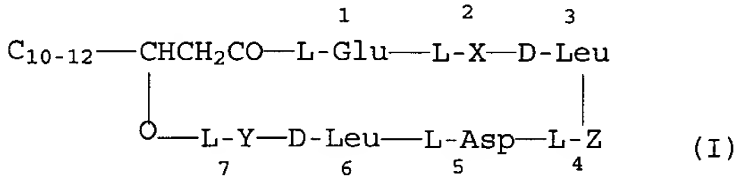
The results of the Examples demonstrate that with the present invention, the product isolated from blood or a biotechnologically produced product is rendered substantially free of lipid-enveloped viruses, by reducing the viral titer by a factor of $>10^4$.

2) Inherency with Itokawa et al. - The Examiner asserts that due to the overlap of concentrations, Itokawa et al. must necessarily be practicing the present invention. Applicants respectfully disagree with this position.

Itokawa et al. does not disclose either explicitly or inherently the presently claimed method of rendering a purified product isolated from blood or a biotechnologically produced product substantially free of lipid-enveloped viruses by reducing the viral titer by a factor of approximately $>10^4$ in a short time of only 30 minutes to 2 hours. Under the doctrine of inherency, if an element is not expressly disclosed in a prior art reference, the reference will only be deemed to anticipate a subsequent claim if one skilled in the art would "read" the reference as inherently disclosing the element. Rosco, Inc. v. Mirror Lite Co. Nos. 01-1271, -1302 (Fed. Cir. decided Sept. 24, 2002). Upon reading Itokawa et al., one skilled in the art would not consider the cyclic lipoheptapeptides used in the present invention for the effective complete removal of viruses in products, given the

disclosure in Itokawa et al. of a "moderate HIV-activity." As such, Itokawa et al. does not disclose the present invention and withdrawal of the rejection is respectfully requested.

3) **Pauli declaration** - The Examiner finds the Pauli declaration insufficient to overcome the rejection over Naruse et al. The present claims have been amended to define the cyclic lipopetide used in the recited method as being of the following formula (I)



(I)

a salt, ester or mixture thereof,

wherein in the formula (I), X and Y each independently represent the amino acids Leu, Ile or Val, Z represents the amino acids Val or Ala, and C_{10-12} represents a linear or branched, saturated alkyl group.

Naruse et al. fails to disclose the above-recited cyclic lipopeptide of the present invention. In addition, Naruse et al. fails to disclose a method of rendering a purified product isolated from blood or a biotechnologically produced product substantially free of lipid-enveloped viruses by reducing the viral titer by a factor of approximately $>10^4$, in a short time of

only 30 minutes to 2 hours, at room temperature. As such, Naruse et al. fails to disclose the present invention and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner had previously rejected claims 1-9, 13-15, 18 and 19 under 35 U.S.C. §112, second paragraph as being indefinite because no units are included. Applicants addressed this issue in the response filed on June 4, 2002, which the Examiner entered. The Examiner did not indicate in the Advisory Action that the rejection had been withdrawn. Since the Examiner also did not rebut Applicants' arguments, Applicants believe that the rejection has been withdrawn. However, clarification of the issue is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph for lack of enablement

Claims 1-10, 13-15, 18 and 19 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement. More specifically, the Examiner asserts that the invention is not enabled for the preparation of products for *in vivo* administration. The Examiner asserts that the agents used in the present invention are known to be toxic and damaging to blood

cells. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The present invention is drawn to a method of inactivating lipid-enveloped viruses in purified biological products or biotechnologically produced products. The present invention is not drawn to a method of administering products in vivo. The Examiner asserts that "applicants claims encompass any and all biological products...for *in* vivo administration." Applicants again note that present invention does not claim products or therapeutic methods. The present invention claims a method of directly inactivating viruses in a cell-free biological product. Applicants have clearly demonstrated such inactivation with the experiments in the specification. As such, the rejection of the claims is misplaced and not relevant to the claimed invention. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph - new matter

Claims 1-11, 13-15, 18 and 19 have been rejected under 35 U.S.C. §112, first paragraph as adding new matter with regard to the recitation of "cell-free" biological product. In the Advisory Action, the Examiner asserts that the disclosure of albumin does not provide adequate support for "cell-free." Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Claims 1 and 18 have been amended to recite "a purified product isolated from blood or a biotechnologically produced product." Support for these amendments may be found on pages 27, first paragraph, page 9 and page 2, lines 3-6. Claim 2 has been amended to be consistent with claim 1. As such, no new matter has been added with these amendments. Withdrawal of the rejection is respectfully requested.

If any questions remain regarding the above matters, please contact Applicant's representative, MaryAnne Armstrong, PhD (Reg. No. 40,069), in the Washington metropolitan area at the phone number listed below.

A marked-up version of the amended claims showing all changes is attached hereto.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a response in connection with the present application. The required fee is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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MARKED-UP VERSION SHOWING CHANGES

IN THE CLAIMS

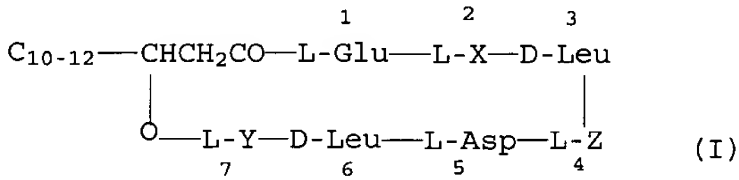
Claim 19 has been cancelled.

Claims 1, 2 and 18 have been amended as follows.

1. (Four Times Amended) A method of **rendering a purified product isolated from blood or a biotechnologically produced product substantially free of** ~~inactivating~~ lipid-enveloped viruses ~~in a cell free biological product~~ **by reducing the viral titer by a factor of approximately $>10^4$**, which comprises

~~providing a cyclic lipopeptide, a salt of the lipopeptide, an ester of the lipopeptide, or a mixture thereof;~~

contacting said product **with a cyclic lipoheptapeptide of the following formula (I)**



(I)

a salt, ester or mixture thereof,

wherein in the formula (I), X and Y each independently represent the amino acids Leu, Ile or Val, Z represents the amino acids Val or Ala, and C_{10-12} represents a linear or branched, saturated alkyl group,

~~with the cyclic lipopeptide, salt of the lipopeptide, ester~~

~~of the lipopeptide, or mixture thereof as an inactivating agent,~~ **wherein said product is contacted with said cyclic lipoheptapeptide** at room temperature for 30 minutes up to 2 hours, **and**

wherein ~~the agent~~ **said cyclic lipoheptapeptide** is added to said product at a concentration of 1-100 μM ~~and viral titer is reduced by a factor of >10^4 through the direct inactivation of any lipid enveloped viruses present in said product by the agent~~.

2. (Twice Amended) The method of claim 1, **wherein said product is contacted** ~~characterized in that the virus inactivation in biological products is performed~~ at temperatures higher than room temperature, within a period of 5-30 min.

18. (Twice Amended) The method of claim 1, wherein the **biotechnologically produced product** ~~cell free biological~~ product is selected from the group consisting of **vaccines, monoclonal antibodies, hormones and recombinant proteins** ~~products isolated from blood, and biotechnological pharmaceutical products consisting of human proteins~~.